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Commentary

Integrating complex genomic datasets and tumour cell sensitivity profiles to address a 'simple' question: which patients should get this drug?

Cyril Benes and Jeff Settleman*

Address: Center for Molecular Therapeutics, Massachusetts General Hospital Cancer Center and Harvard Medical School, 149 13th Street, Charlestown, MA 02129, USA

Email: Cyril Benes - cbenes@bidmc.harvard.edu; Jeff Settleman* - settleman@helix.mgh.harvard.edu

* Corresponding author

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Abstract

It is becoming increasingly apparent that cancer drug therapies can only reach their full potential through appropriate patient selection. Matching drugs and cancer patients has proven to be a complex challenge, due in large part to the substantial molecular heterogeneity inherent to human cancers. This is not only a major hurdle to the improvement of the use of current treatments but also for the development of novel therapies and the ability to steer them to the relevant clinical indications. In this commentary we discuss recent studies from Kuo *et al*., published this month in *BMC Medicine*, in which they used a panel of cancer cell lines as a model for capturing patient heterogeneity at the genomic and proteomic level in order to identify potential biomarkers for predicting the clinical activity of a novel candidate chemotherapeutic across a patient population. The findings highlight the ability of a 'systems approach' to develop a better understanding of the properties of novel candidate therapeutics and to guide clinical testing and application.

See the associated research paper by Kuo et al: http://www.biomedcentral.com/1741-7015/7/77

Commentary

The clinical benefit associated with virtually all cancer drugs is typically limited to a fraction of treated patients. Unfortunately, for most of these drugs, the basis for such a variable response to treatment is poorly understood [1]. The recent emergence of so-called 'rationally-targeted' agents, such as the kinase-targeted inhibitors, trastuzumab (anti-HER2 antibody) and the small molecule kinase inhibitors erlotinib (EGFR) and imatinib (BCR-ABL, PDGFR and c-KIT), has led to significant insights into the role of the genomic features of tumour cells in determining the clinical response to these treatments. It has also highlighted the substantial heterogeneity that exists across patient populations with respect to the tumour genome [2-4]. For this class of inhibitors, activating mutations affecting the kinase target have proven to be the most reliable predictors of drug response identified thus far [5-9]. Such findings have prompted substantial efforts to better understand the relationship between specific tumour genotypes and the clinical response to a variety of established and investigational cancer drugs in order to prospectively identify patient cohorts who are most likely to derive clinical benefit from a particular therapeutic [10-14].

However, the identification of 'drug-sensitizing genotypes' for the relatively non-specific conventional chemotherapy drugs has been more challenging. While these agents still constitute the mainstay of first-line cancer drug

therapy for many clinical indications, their precise mechanisms of action remain poorly understood which thus challenges efforts to identify the specific genomic determinants of variable treatment response. One approach to this problem has been to interrogate the state of the tumour genome more broadly by exploiting, for example, genome-wide microarray-based expression profiling [15]. Such gene expression profiles, or signatures, can potentially capture complex cellular states that are likely to reflect a mixture of genomic features that vary between tumours and which are associated with both mutational and epigenetic distinctions [16]. Indeed, several such gene signatures, for both predictive and prognostic assessment of patient outcomes, have emerged from pre-clinical as well as clinical studies and a few have now been approved for clinical use [15,17,18]. In addition, a variety of additional forms of systems information, including genomic copy number data, proteomic and phospho-proteomic data, and, more recently, metabolomic information, can all potentially be used to identify distinctions among human tumours that relate to prognosis and treatment response.

In the accompanying report published this month in *BMC Medicine*, Kuo and coworkers present a systems analysis of the sensitivity of a panel of human breast cancer-derived cell lines to a polyamine analogue (PG-11047) currently undergoing early phase clinical testing in cancer [19]. Polyamines are naturally present at relatively high concentrations in all cell types, where they are essential components of nucleic acid metabolism and a variety of fundamental cellular processes [20]. Since the enzymes regulating polyamine synthesis and catabolism are frequently dysregulated in human tumours, they have been considered as potential targets for anti-cancer drug development [21]. The authors had previously established and characterized a collection of breast cancer cell lines as a model system for examining therapeutic efficacy and its relationship to specific genomic features [22]. Although the validity of cell line-based approaches to inform clinical decisions has been the subject of debate for many years, such approaches have recently shown great potential in revealing the genomic basis of anti-cancer drug response [22-26].

Using a panel of 48 genomically characterized human breast cancer cell lines, Kuo *et al*. identified a set of 250 genes whose expression, as assessed by whole genome microarray analysis, was associated with PG-11047 sensitivity in an *in vitro* growth inhibition assay. Then, using a bioinformatics tool called Ingenuity Pathway Analysis, they found that this gene set was enriched for genes associated with interferon response, suggesting that interferon signalling might affect sensitivity to polyamine analogues. This gene set was then further refined through a Monte Carlo cross-validation approach to a list of 13 genes - a manageable number with respect to the evaluation of clinical specimens - and this 13 gene set was found to be predictive of cell line sensitivity to PG-11047. The analysis revealed several findings of potential interest. First, it was observed that cell lines from the basal tumour subtype were more sensitive to PG-11047 than cells from tumours of luminal origin. By applying their classifier to a panel of breast tumour samples, the authors observed that basal tumours were, indeed, predicted to be more sensitive than luminal tumours, suggesting that PG-11047 should potentially be directed to patients with tumours of basal subtype, which is the more aggressive tumour type. Finally, they found that elevated levels of the cellular survival signalling protein, phospho-AKT, were associated with increased PG-11047 sensitivity. Thus, the collective analysis revealed several features of breast tumour cells that may be relevant to their response to PG-11047.

This analysis nicely illustrates how the integration of multiple forms of system wide information with drug sensitivity profiles assessed *in vitro* using cancer-derived cell lines can begin to penetrate the complexity of human tumours. Recent advances in genomic and proteomic technologies [27-29] have led to the establishment of increasingly complex data sets; the use of computational modelling strategies [30] to link such information to drug sensitivity profiles has the potential to substantially enhance our understanding of pharmacologic mechanisms. The ability of the gene signature identified by Kuo *et al*. to facilitate patient selection and to increase the likelihood of a positive clinical outcome remains to be tested. However, this study constitutes a significant step towards the establishment of genomic analysis as a broadly useful strategy for stratifying patients for treatment with agents whose mechanism of action remains poorly understood.

Competing interests

The authors declare that they have no competing interests.

References

1. Walther A, Johnstone E, Swanton C, Midgley R, Tomlinson I, Kerr D: **Genetic prognostic and predictive markers in colorectal cancer.** *Nat Rev Cancer* 2009, **9:**489-499.
2. Druker BJ: **Perspectives on the development of imatinib and the future of cancer research.** *Nat Med* 2009, **15:**1149-1152.
3. Nahta R, Esteva FJ: **Trastuzumab: triumphs and tribulations.** *Oncogene* 2007, **26:**3637-3643.
4. Janne PA, Gray N, Settleman J: **Factors underlying sensitivity of cancers to small-molecule kinase inhibitors.** *Nat Rev Drug Discov* 2009, **8:**709-723.
5. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, *et al.*: **Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2.** *N Engl J Med* 2001, **344:**783-792.
6. Tuveson DA, Weber BL, Herlyn M: **BRAF as a potential therapeutic target in melanoma and other malignancies.** *Cancer Cell* 2003, **4:**95-98.
7. Collisson EA, De A, Suzuki H, Gambhir SS, Kolodney MS: **Treatment of metastatic melanoma with an orally available inhib-**

itor of the Ras-Raf-MAPK cascade. *Cancer Res* 2003, **63:**5669-5673.
8. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, *et al.*: **Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib.** *N Engl J Med* 2004, **350:**2129-2139.
9. Paez JG, Janne PA, Lee JC, Tracy S, Greulich H, Gabriel S, Herman P, Kaye FJ, Lindeman N, Boggon TJ, *et al.*: **EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy.** *Science* 2004, **304:**1497-1500.
10. Eberhard DA, Johnson BE, Amler LC, Goddard AD, Heldens SL, Herbst RS, Ince WL, Janne PA, Januario T, Johnson DH, *et al.*: **Mutations in the epidermal growth factor receptor and in KRAS are predictive and prognostic indicators in patients with non-small-cell lung cancer treated with chemotherapy alone and in combination with erlotinib.** *J Clin Oncol* 2005, **23:**5900-5909.
11. Tsao MS, Sakurada A, Cutz JC, Zhu CQ, Kamel-Reid S, Squire J, Lorimer I, Zhang T, Liu N, Daneshmand M, *et al.*: **Erlotinib in lung cancer - molecular and clinical predictors of outcome.** *N Engl J Med* 2005, **353:**133-144.
12. Berns K, Horlings HM, Hennessy BT, Madiredjo M, Hijmans EM, Beelen K, Linn SC, Gonzalez-Angulo AM, Stemke-Hale K, Hauptmann M, *et al.*: **A functional genetic approach identifies the PI3K pathway as a major determinant of trastuzumab resistance in breast cancer.** *Cancer Cell* 2007, **12:**395-402.
13. Engelman JA, Chen L, Tan X, Crosby K, Guimaraes AR, Upadhyay R, Maira M, McNamara K, Perera SA, Song Y, *et al.*: **Effective use of PI3K and MEK inhibitors to treat mutant Kras G12D and PIK3CA H1047R murine lung cancers.** *Nat Med* 2008, **14:**1351-1356.
14. Ihle NT, Lemos R Jr, Wipf P, Yacoub A, Mitchell C, Siwak D, Mills GB, Dent P, Kirkpatrick DL, Powis G: **Mutations in the phosphatidylinositol-3-kinase pathway predict for antitumor activity of the inhibitor PX-866 whereas oncogenic Ras is a dominant predictor for resistance.** *Cancer Res* 2009, **69:**143-150.
15. van't Veer LJ, Dai H, Vijver MJ van de, He YD, Hart AA, Mao M, Peterse HL, Kooy K van der, Marton MJ, Witteveen AT, *et al.*: **Gene expression profiling predicts clinical outcome of breast cancer.** *Nature* 2002, **415:**530-536.
16. Cole KA, Krizman DB, Emmert-Buck MR: **The genetics of cancer--a 3D model.** *Nat Genet* 1999, **21:**38-41.
17. Simon R: **The use of genomics in clinical trial design.** *Clin Cancer Res* 2008, **14:**5984-5993.
18. Ross JS, Hatzis C, Symmans WF, Pusztai L, Hortobagyi GN: **Commercialized multigene predictors of clinical outcome for breast cancer.** *Oncologist* 2008, **13:**477-493.
19. Kuo WL, Das D, Ziyad S, Bhattacharya S, Gibb WJ, Heiser LM, Sadanandam A, Fontenay GV, Hu Z, Wang NJ, Bayani N, Feiler HS, Neve RM, Wyrobek AJ, Spellman PT, Marton LJ, Gray JW: **A systems analysis of chemosensitivity of breast cancer cells to the polyamine analogue PG-11047.** *BMC Medicine* 2009, **7:**77.
20. Gerner EW, Meyskens FL Jr: **Polyamines and cancer: old molecules, new understanding.** *Nat Rev Cancer* 2004, **4:**781-792.
21. Casero RA Jr, Marton LJ: **Targeting polyamine metabolism and function in cancer and other hyperproliferative diseases.** *Nat Rev Drug Discov* 2007, **6:**373-390.
22. Neve RM, Chin K, Fridlyand J, Yeh J, Baehner FL, Fevr T, Clark L, Bayani N, Coppe JP, Tong F, *et al.*: **A collection of breast cancer cell lines for the study of functionally distinct cancer subtypes.** *Cancer Cell* 2006, **10:**515-527.
23. McDermott U, Sharma SV, Dowell L, Greninger P, Montagut C, Lamb J, Archibald H, Raudales R, Tam A, Lee D, *et al.*: **Identification of genotype-correlated sensitivity to selective kinase inhibitors by using high-throughput tumor cell line profiling.** *Proc Natl Acad Sci USA* 2007, **104:**19936-19941.
24. McDermott U, Sharma SV, Settleman J: **High-throughput lung cancer cell line screening for genotype-correlated sensitivity to an EGFR kinase inhibitor.** *Methods Enzymol* 2008, **438:**331-341.
25. Godin-Heymann N, Ulkus L, Brannigan BW, McDermott U, Lamb J, Maheswaran S, Settleman J, Haber DA: **The T790M 'gatekeeper' mutation in EGFR mediates resistance to low concentrations of an irreversible EGFR inhibitor.** *Mol Cancer Ther* 2008, **7:**874-879.
26. Sos ML, Michel K, Zander T, Weiss J, Frommolt P, Peifer M, Li D, Ullrich R, Koker M, Fischer F, *et al.*: **Predicting drug susceptibility of non-small cell lung cancers based on genetic lesions.** *J Clin Invest* 2009, **119:**1727-1740.
27. Jones PA, Baylin SB: **The epigenomics of cancer.** *Cell* 2007, **128:**683-692.
28. Kohn EC, Lu Y, Wang H, Yu Q, Yu S, Hall H, Smith DL, Meric-Bernstam F, Hortobagyi GN, Mills GB: **Molecular therapeutics: promise and challenges.** *Semin Oncol* 2004, **31:**39-53.
29. Rikova K, Guo A, Zeng Q, Possemato A, Yu J, Haack H, Nardone J, Lee K, Reeves C, Li Y, *et al.*: **Global survey of phosphotyrosine signaling identifies oncogenic kinases in lung cancer.** *Cell* 2007, **131:**1190-1203.
30. Janes KA, Yaffe MB: **Data-driven modelling of signal-transduction networks.** *Nat Rev Mol Cell Biol* 2006, **7:**820-828.

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